Copper-catalyzed enantioselective synthesis of trans-1-Alkyl-2-substituted cyclopropanes via tandem conjugate addition-intramolecular enolate trapping

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Copper-Catalyzed Enantioselective Synthesis of *trans*-1-Alkyl-2-substituted Cyclopropanes via Tandem Conjugate Addition−Intramolecular Enolate Trapping

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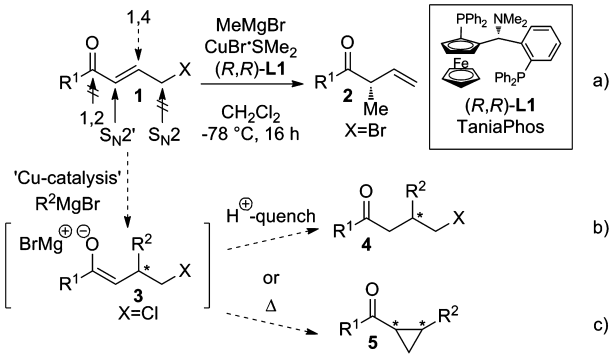
Abstract: Cu-TolBINAP-catalyzed conjugate addition of Grignard reagents to 4-chloro-α,β-unsaturated esters, thioesters, and ketones leads to 4-chloro-3-alkyl-substituted thioesters and ketones in up to 84% yield and up to 96% ee upon protonation of the corresponding enolates at low temperature. Tandem conjugate addition−enolate trapping, however, yields *trans*-1-alkyl-2-substituted cyclopropanes in up to 92% yield and up to 98% ee. The versatility of this reaction is illustrated by the formation of key intermediates for the formal syntheses of cascarillic acid and grenadamide.

The enantioselective Simmons−Smith cyclopropanation with a stoichiometric amount of a chiral dioxaborolane, introduced by Charette and co-workers,[1] is currently the benchmark reaction for the synthesis of *trans*-1-alkyl-2-substituted cyclopropanes. Only a few catalytic[2] asymmetric methods[3,4] can compete with this method[1] in terms of efficiency and yield. This is in sharp contrast to the well-known catalytic asymmetric synthesis of *trans*-1-aryl-2-substituted cyclopropanes.[5,6] Although Michael addition-initiated ring-closure reactions (MIRCs) are well-known for the diastereo- and enantioselective preparation of substituted cyclopropanes,[5] to the best of our knowledge the use of organometallic reagents for the catalytic asymmetric[6,7] preparation of *trans*-1,2-disubstituted cyclopropanes[6a,b,e,l] via MIRC is unprecedented in the literature.[8]

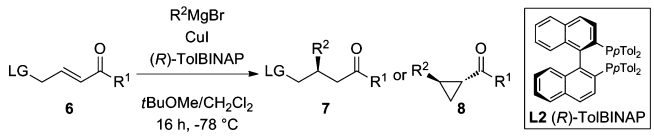
Recently, we explored the asymmetric allylic alkylation[9] of 4-halocrotonates using Grignard reagents for the preparation of α-Me-substituted ester **2** in high yield and high regio- and enantioselectivity (Scheme 1a, R^1 = OBn).[10] Here we report the Cu-catalyzed asymmetric 1,4-addition (ACA) of Grignard reagents[9b,c,11] to 4-chlorocrotonates using the readily available TolBINAP as ligand. This transformation provides a route to 4-chloro-3-alkyl-substituted thioesters and ketones (Scheme 1b, **4**, X = Cl) and a general method to form *trans*-1,2-disubstituted cyclopropanes (Scheme 1c, **5**, X = Cl) with excellent enantioselectivities.

Scheme 1. Switch in Regioselectivity for the Reactions of 4-Halocrotonates with Grignard Reagents



To synthesize *trans*-cyclopropanes via tandem ACA−enolate trapping, initially the ACA of Grignard reagents to 4-halocrotonates was studied while varying the ligand (Table 1). The low yield observed[12] for the ACA to bromo-substituted thioester **6a** (entry 1) prompted us to investigate the chloro-substituted analogue **6b** for this reaction (entry 2). Addition of hexylmagnesium bromide to **6b** using Cu-TolBINAP at −78 °C gave, after quenching at this temperature, 4-chloro-3-hexyl thioester **7b** in good yield (83%) and excellent ee (94%). For 4-halo-α,β-unsaturated aliphatic ketones and esters, similar results were obtained. For instance, reactions of the bromo-substituted substrates **6c** and **6d** with Grignard reagents gave low yields of, respectively, cyclopropanes **8c** and **8d** (entries 3 and 4). In contrast, the reaction of the 4-chloro-substituted α,β-unsaturated ketone **6e** gave **7e** in good yield (entry 5, 84%) and excellent ee (96%). The Cu-catalyzed reaction of ester **6f** with phenethylmagnesium bromide at −40 °C gave cyclopropane **8f** as the main product, along with traces of **7f**, in a reasonable yield (65%, entry 6) and excellent ee (>95%). Already at −40 °C, the enolate formed from **6f** undergoes slow ring-closure to yield the corresponding cyclopropane, **8f**.

Table 1. Substrate Screening for ACA to 4-Halocrotonates[a]

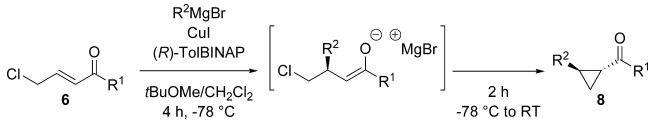


entry	LG		R^1	R^2	product	yield (%)	ee[b] (%)
1	Br	**6a**	SEt	hexyl	**8a**	<20[c]	−
2	Cl	**6b**	SEt	hexyl	**7b**	83	94
3	Br	**6c**	$C_{11}H_{23}$	hexyl	**8c**	32[d]	n.d.
4[e]	Br	**6d**	OMe	$BnCH_2$	**8d**	<20[c]	−
5	Cl	**6e**	$C_{11}H_{23}$	$BnCH_2$	**7e**	84	96
6[e]	Cl	**6f**	OMe	$BnCH_2$	**8f**[f]	65[g]	>95

[a] Conditions: **6** (0.5 mmol) in CH_2Cl_2 added over 2 h to a solution of CuI (1 mol %), TolBINAP (1.5 mol %), and Grignard reagent (1.2 equiv) in *t*BuOMe. [b] Determined by chiral GC or HPLC. [c] Based on GC−MS. [d] 20% of **6c** and 18% of (*E*)-pentadec-2-en-4-one obtained. [e] Reaction performed at −40 °C, 4 h reaction time. [f] In addition, traces (<10%) of **7f** were obtained; in all other entries, exclusively **7** or **8** was obtained. [g] Combined yield of **7f** and **8f**.

The formation of cyclopropanes via tandem ACA−enolate trapping was subsequently investigated. The reaction of hexylmagnesium bromide and **6b**, after completion of the ACA and warming to room temperature, afforded the diastereomerically pure *trans*-cyclopropane **8b** in high yield (Table 2, entry 1). Both **7b** and **8b** were obtained with 94% ee. However, precise control of the amount of Grignard reagent is essential to obtain good yields of the cyclopropanes. When less than 1.2 equiv of hexylmagnesium bromide was used, a small but significant

Table 2. Scope of Alkyl Grignard Reagents and Electron-Withdrawing Groups for Tandem ACA−Enolate Trapping toward *trans*-Cyclopropanes[a]



entry	R^1		R^2	product	yield (%)	ee[b] (%)
1	SEt	**6b**	hexyl	**8b**	87	94
2	SEt	**6b**	Me	**8g**	56	87
3	SEt	**6b**	Et	**8h**	67	95
4	SEt	**6b**	*i*Pr	**8i**	89	70
5	SEt	**6b**	*i*Bu	**8j**	91	84
6[c]	SEt	**6b**	but-3-enyl	**8k**	88	94
7[d]	SEt	**6b**	$(CH_2)_3O$*t*Bu	**8l**	>95[d]	96
8	SEt	**6b**	$BnCH_2$	**8m**	92	84
9[d]	SEt	**6b**	Ph	**8n**	50	26
10	$C_{11}H_{23}$	**6e**	$BnCH_2$	**8e**	75	96
11	$C_{11}H_{23}$	**6e**	Me	**8o**	87	98
12	OMe	**6f**	$BnCH_2$	**8f**	68	>95

[a] For conditions see Table 1, 1.0 mmol scale. [b] Determined by chiral GC or HPLC. [c] 3.0 mmol scale. [d] Conversion; the cyclopropane proved inseparable by column chromatography from the dimer of the Grignard reagent. [e] 0.5 mmol scale.

amount of acyclic product **7b** was obtained. When more than 1.2 equiv of the Grignard reagent was used, the corresponding cyclopropane bearing a tertiary alcohol was formed, as a result of a subsequent two-fold addition of the Grignard reagent to the thioester moiety.

With the procedure for the synthesis of *trans*-cyclopropanes developed, the scope of the alkyl Grignard reagents for this transformation was explored. The use of both MeMgBr and EtMgBr gave the corresponding volatile *trans*-cyclopropanes **8g** and **8h** with good to excellent ee (entries 2 and 3). The Cu-catalyzed transformation of **6b** with the sterically encumbered Grignard reagents *i*PrMgBr and *i*BuMgBr gave the corresponding cyclopropanes **8i** and **8j** in slightly lower ee but high yield (entries 4 and 5). The catalytic asymmetric synthesis of cyclopropanes using functionalized Grignard reagents includes those substituted with olefin, ether, and aryl groups. These functionalized Grignard reagents gave cyclopropanes **8k**, **8l**, and **8m** with ee's ranging from 84 to 96% (entries 6−8). Finally, when PhMgBr was used the product **8n** was obtained in both low yield and ee (entry 9).

Ketone substrate **6e** gave, upon allowing the reaction mixture to reach room temperature, the corresponding cyclopropane with 96% ee (Table 2, entry 10). The reaction of **6e** with MeMgBr gave cyclopropane **8o** in excellent yield and 98% ee (entry 11). When the reaction mixture of **6f** and phenethylmagnesium bromide was allowed to warm to room temperature, exclusively cyclopropane **8f** was obtained, virtually enantiomerically pure (entry 12).

To illustrate the versatility of the developed method, cyclopropane **8b** was selectively reduced to the aldehyde (see Supporting Information, SI Scheme 1), which is a key intermediate in a reported synthesis[13] of cascarillic acid.[14,15] Furthermore, the reaction of **6b** with heptylmagnesium bromide gave cyclopropane **8p** in 84% yield and 95% ee. Reduction of **8p** to the corresponding aldehyde then gave an intermediate for the synthesis[16] of grenadamide.[17,18]

In summary, a new and versatile enantioselective synthesis of 4-chloro-3-alkyl-substituted thioesters and ketones and *trans*-1-alkyl-2-substituted cyclopropane esters, thioesters, and ketones has been developed using an extremely simple catalytic system, based on a commercial chiral ligand, CuI, and Grignard reagents. Application of this methodology in natural product synthesis and other ring structures will be reported in due course.

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Supporting Information Available: Experimental details, data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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